The specification has been further amended to include sequence identifiers and a Sequence Listing. Entry of the Sequence Listing does not raise the issue of new matter as the sequence information contained therein is presented in the application as originally filed. The computer readable copy of the Sequence Listing submitted herewith is the same as the attached paper copy of that Listing.

Claim 16 has been revised so as to be placed in independent form. Claims 3-10, 12, 13, 15 and 17 as presented depend directly or indirectly from claim 16. Claims 1, 2, 11, 14 and 18-27 have been cancelled. That the claims have been revised/cancelled should not be taken as an indication that Applicants agree with any view expressed by the Examiner. Rather, the revisions have been made merely to advance prosecution and Applicants reserve the right to pursue any deleted subject matter in a continuation application.

Claims 16 and 17 stand rejected under 35 USC 101 as allegedly lacking utility. The rejection is respectfully traversed.

The Examiner contends that there is no "specific and substantial" utility for the claimed immunogen and no disclosure to the type of immune response expected and what usefulness any such response may have. The Examiner takes

the position that while it is interesting that H2 binds H1 when envelope protein is bound to ligand, this allegedly has no patentable utility.

The Examiner's assertions to the contrary, the disclosure clearly teaches that the claimed immunogen induces broadly reactive neutralizing antibodies necessary for an effective AIDS vaccine. In accordance with the invention, the immunogen comprises an HIV envelope protein that has been activated to expose intermediate conformations of conserved neutralization epitopes that are normally only transiently or less well exposed on the surface of the HIV virion. The immunogen is a frozen triggered form of the HIV envelope that makes available specific epitoptes for presentation to B lymphocytes. The result of this epitope presentation is the production of antibodies that broadly neutralize HIV.

The gp41 HR-2 region peptides (for example, DP-178 and T-649 Q262) "freeze" fusogenic epitopes. Importantly, when added to a triggered envelope, such peptides result in prevention of fusion (see Figures 9 and 13).

It will be clear from the foregoing that the claimed invention is, in fact, supported by a specific and substantial utility. Respectfully, the Examiner's

assertions relating to the shielding of H1 by the addition of H2 peptide overlook the fundamentals of the invention.

Reconsideration is requested.

Claims 16 and 17 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The terminology used in the claims is fully understood by those skilled in the art (see, for example Kwong et al, Nature 393:648 (1998) of record). That being the case, no indefiniteness results from the present language, which is in no way arbitrary.

As regards the term "upregulates", the Examiner's attention is directed to page 17, line 19, which reads "upregulation (exposure)".

In view of the above, reconsideration is requested.

Claims 16 and 17 stand rejected under 35 USC 112, first paragraph. This rejection is clearly related to the rejection under 35 USC 101 above and should be withdrawn for the reasons provided in response to the rejection based on lack of utility. Reconsideration is requested.

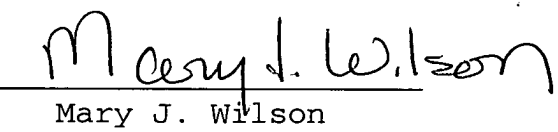
Attached hereto is a marked-up version of the changes made to the specification and claims by the current

amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE, P.C.

By 
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at page 24, line 10:

Synthetic peptides were synthesized (SynPep Corporation, Dublin, CA), and purified by reverse phase HPLC. Peptides used in this study had greater than 95% purity as determined by HPLC, and confirmed to be correct by mass spectrometry. The CCR5-D1 (MDYQVSSPIYDINYYTSEPCQKINVKQIAAR) (SEQ ID NO:1), peptide was derived from the N-terminus of human CCR5 (Bieniasz et al, EMBO Journal 16:2599-2609 (1997)). Gp41 peptides DP-178 YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF (SEQ ID NO:2) (Wild et al, Proc. Natl. Acad. Sci. USA 91:12676-12680 (1994)), T-649 WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL (SEQ ID NO:3) (Rimsky et al, J. Virol. 72:986-993 (1998)), and T649-Q26L (WMEWDREINNYTSLIHSLIEESQNQLEKNEQELLEL) (SEQ ID NO:4) (Shu et al, Biochemistry 39:1634-1642 (2000)) were derived from HIV-1 envelope gp41 from HIV 89.6 (Collmann et al, J. Virol. 66:7517-7521 (1992)). As a control for HR-2 peptide binding, a scrambled sequence DP178 peptide was made as well.

The paragraph beginning at page 36, line 7:

Neutralizing Epitopes on HIV 89.6 gp140 Before and After Ligation with sCD4. The 2F5 (anti-gp41, ELDKWAS (SEQ ID NO:5)) (Muster et al, J. Virol. 67:6642-6647 (1993)), mab neutralizes HIV primary isolates. Prior to ligation of cleaved 89.6 gp140 with sCD4, it was found that the 2F5 gp41 epitope was exposed. Following sCD4 ligation, the 17b CCR5 binding site epitope (2-4) was upregulated and the 2F5 epitope continued to be expressed.

The paragraph beginning at page 37, line 19:

HR-2 Peptides. Synthetic peptides were synthesized (SynPep, Inc., Dublin, CA), and purified by reverse phase HPLC. Peptides used in this study had greater than 95% purity as determined by HPLC, and confirmed to be correct by mass spectrometry. gp41 peptides DP178, YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF (SEQ ID NO:2) (Wild et al, Proc. Natl. Acad. Sci. USA 19:12676-12680 (1994)), and T649-Q26L, WMEWDREINNYTSLIHSLIEESQNQLEKNEQELLEL (SEQ ID NO:4) (Rimsky et al, J. Virol. 72:986-993 (1998), Shu et al, Biochemistry 39:1634-1642 (2000)) were derived from HIV-1 envelope gp41 from HIV 89.6 (Collman et al, J. Virol. 66:7517-7521 (1992)). As a control for HR-2 peptide

binding, a scrambled sequence DP178 peptide was made. For immunoprecipitations and select SPR experiments, biotinylated DP178 and DP178 scrambled peptides were synthesized (SynPep, Inc.).

IN THE CLAIMS:

3. (Amended) The immunogen according to claim [1] 16 wherein said ligand is an antibody, or Fab_2 or Fab fragment thereof.

4. (Amended) The immunogen according to claim [2] 16 wherein said ligand binds to a CCR5 binding site on gp120 and upregulates a CD4 binding site on gp120.

7. (Amended) The immunogen according to claim [1] 16 wherein said ligand upregulates a CCR5 and a CD4 binding site on gp120.

12. (Amended) The immunogen according to claim [1] 16 wherein said protein is in soluble form.

13. (Amended) The immunogen according to claim [1] 16 wherein said protein is associated with a cell vesicle or liposome.

15. (Amended) The immunogen according to claim [14] 16 wherein gp120, gp41 and said ligand are crosslinked.

16. (Amended) [The immunogen according to claim 14] An isolated immunogen comprising an HIV envelope protein bound to a ligand, which ligand upregulates at least one of the CD4 binding site and the CCR5 binding site on said protein,

wherein said protein is gp120 noncovalently bound to gp41, and

wherein said immunogen further comprises an HR-2 peptide bound to said protein.